REMARKS

I. Status Summary

Claims 1, 2, 6, and 8 are pending in the present U.S. patent application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

The Information Disclosure Statement (IDS) filed May 26, 2005 has been objected to in part upon the contention that the IDS does not comply with 37 C.F.R. 1.98.

Claims 1, 2, and 6 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are unpatentable over Liu *et al.* (88 *J Pharmaceutical Sci* 1161-1168, 1999; hereinafter "Liu").

Claims 1, 2, 6, and 8 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are obvious over Liu.

Claim 2 has been canceled. Claim 1 has been amended. Support for the amendment can be found throughout the specification as filed, including *inter alia* in Figure 2A, which shows straight chain alkylphosphocholines of, in some embodiments, 13 to 20 methylene groups. Additional support can be found in the Examples and in Table 2.

Reconsideration of the application based on the remarks set forth below is respectfully requested.

II. Response to the Objection to the IDS

The IDS filed May 26, 2005 has been objected to in part upon the contention that the IDS does not comply with 37 C.F.R. 1.98. Particularly, the Patent Office asserts that the listing of the Written Opinion for PCT/US01/31501 dated October 29, 2004 (hereinafter "the Written Opinion") does not comply with 37 C.F.R. 1.98, as the Written Opinion is not a publication per se.

In response to the objection, applicants respectfully submit that the Written Opinion disclosed no references that had not been already been disclosed to the Patent Office by applicants. More particularly, the Written Opinion cited only Liu, which was disclosed by applicants in a Supplemental IDS filed May 27, 2003, and U.S. Patent No. 5,144,045 to Wissner *et al.*, which was disclosed to the Patent Office in an IDS filed July 18, 2002. As such, applicants respectfully submit that the Written Opinion was included in the IDS filed

May 26, 2005 in an abundance of caution solely to inform the Patent Office that a Written Opinion had been received for the corresponding PCT International Patent Application.

Therefore, applicants respectfully submit that since the Patent Office has determined that disclosure of the Written Opinion is not required, and further because the references disclosed therein are duplicative of references already disclosed to the Patent Office, applicants believe it is unnecessary to file a further Supplemental IDS to replace the objected to IDS. Applicants thus respectfully request that the instant objection be withdrawn at this time.

III. Response to the Rejection under 35 U.S.C. § 102(b)

Claims 1, 2, and 6 have been rejected under 35 U.S.C. § 102(b) upon the contention that the claims are anticipated by Liu. According to the Patent Office, Liu discloses that dodecylphosphocholine (DPC) improves paracellular permeability across the intestinal epithelium.

After careful review of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that claim 2 has been canceled, and thus the instant rejection is believed to be moot as to claim 2.

Furthermore, applicants respectfully submit that claim 1 has been amended to recite *inter alia* a method of enhancing paracellular permeability at an absorption site in a subject, the method comprising (a) administering an effective amount of a phospholipase C inhibitor to a subject at a time in which enhanced paracellular permeability is desired, wherein the phospholipase C inhibitor is selected from an alkylphosphocholine comprising a straight-chain alkyl of 13 to 20 methylene groups. Support for the amendment can be found throughout the specification as filed, including *inter alia* in Figure 2A, which shows straight chain alkylphosphocholines of, in some embodiments, 13 to 20 methylene groups. Additional support can be found in the Examples and in Table 2.

As such, claim 1 recites alkylphosphocholines comprising a carbon chain of 13 to 20 carbon atoms. DPC, on the other hand, has a carbon chain of only 12 carbon atoms. Therefore, it is believed that Liu cannot support a rejection of claim 1 under 35 U.S.C. § 102(b).

Accordingly, applicants respectfully submit that claim 1 has been distinguished over Liu. Claim 6 depends from claim 1, and thus is also believed to be distinguished over Liu. As a result, applicants respectfully request that the rejection of claims 1 and 6 under 35 U.S.C. § 102(b) be withdrawn, and the claims allowed at this time.

IV. Response to the Rejection under 35 U.S.C. § 103(a)

Claims 1, 2, 6, and 8 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Liu. According to the Patent Office, Liu teach that DPC can improve paracellular permeability of certain compounds across the intestinal epithelium. The Patent Office concedes, however, that Liu does not recite improvement of paracellular permeability across the blood brain barrier. Nonetheless, the Patent Office asserts that one of ordinary skill in the art would have appreciated such applicability because of the need to increase the permeability across the blood brain barrier for example with anticancer agents. Thus, the Patent Office contends that the reference suggests and makes *prima facie* obvious how to use the claimed invention at the time the invention was made.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following comments.

Initially, applicants respectfully submit that it appears that the Patent Office is relying on the knowledge that alkylphosphocholines are PLC inhibitors to provide the basis for the assertion that it would have been obvious to use PLC inhibitors generally, and alkylphosphocholines specifically, as therapeutics to enhance paracellular permeability. This connection appears to be based on Liu, which is asserted to teach that dodecylphosphocholine (DPC) can improve paracellular permeability across Caco-2 monolayers by modulating tight junctions.

Applicants respectfully submit, however, that this basis does not suffice to support a rejection under 35 U.S.C. § 103(a). Applicants respectfully submit that at the time of filing, it was not known, and Liu does not teach or suggest, that PLC inhibitors could enhance paracellular permeability and that it is only with reference to the instant specification that the Patent Office can conclude that PLC inhibitors as a class can be used for this purpose. Further, Liu does not teach or suggest that alkylphosphocholines are a class of PLC inhibitors. Thus, it is only with knowledge of applicants' specification that the Patent Office

can assert that any modulating activity disclosed in Liu is derived from DPC's inhibition of PLC.

Since it was unknown at the time of filing of the instant application that DPC's activity in enhancing paracellular permeability resulted from PLC inhibition, applicants respectfully submit that there is no teaching in Liu that would lead one of ordinary skill in the art to believe that PLC inhibitors generally could be used to enhance paracellular permeability as recited in claim 1. Applicants respectfully submit that Liu's demonstration that DPC enhances paracellular permeability does not compel the conclusion that PLC inhibitors generally would enhance paracellular permeability or that alkylphosphocholines, as a class of PLC inhibitors, would enhance paracellular permeability.

In fact, when taken as a whole, Liu clearly states that compounds that had been shown to enhance intestinal absorption of therapeutic molecules were grouped into two main categories: detergents/surfactants and Ca^{2+} chelators. Other agents, such as lysophosphatidylcholines, medium chain fatty acids, and acyl carnitines, were thought to increase paracellular permeability via a mechanism other than Ca^{2+} chelation, hypothesized in Liu to be via upregulation of intracellular Ca^{2+}. As one of the consequences of PLC inhibition would actually be downregulation of intracellular Ca^{2+}, applicants respectfully submit that Liu in fact teaches away from PLC inhibition as a mechanism of action.

Summarily, it appears that the Patent Office is rejecting claims 1, 2, 6, and 8 over Liu on the basis of a demonstration that DPC enhances paracellular permeability, combined with the knowledge found only in applicants' specification that this property is due to DPC's ability to inhibit PLC. Liu does not suggest this mechanism, and in fact suggests instead that the mechanism might involve upregulation of intracellular Ca^{2+}, which would not result from PLC inhibition.

Accordingly, applicants respectfully submit that the Liu reference does not support the rejection of claims 1, 2, 6, and 8 under 35 U.S.C. § 103(a). Claim 2 has been canceled, and thus the rejection is believed to be moot as to this claim. As such, applicants respectfully submit that claims 1, 6, and 8 have been distinguished from Liu, and further that these claims are in condition for allowance at this time. Applicants respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

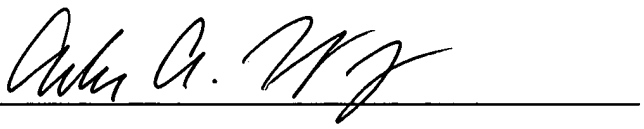
If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge deficiencies in payment of any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: May 12, 2006 By: 

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